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TITLE: Prazosin for Prophylaxis of Chronic Post-Traumatic Headaches in OEF/OIF/OND Service Members and Veterans with Mild TBI

PRINCIPAL INVESTIGATOR: Murray Raskind, MD

CONTRACTING ORGANIZATION: Seattle Institute for Biomedical & Clinical Research
Seattle, WA 98108-1532

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Murray Raskind, MD

E-Mail: murray.raskind@va.gov

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Seattle Institute for Biomedical & Clinical Research
1660 S. Columbian Way
Seattle, WA 98108-1532

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Headaches following combat-related mild traumatic brain injury (mTBI) are common, can be refractory to standard therapies, and may persist and worsen to become a debilitating chronic pain syndrome. The purpose of the proposed study is to evaluate the centrally acting alpha-1 adrenoreceptor antagonist drug prazosin as a prophylactic treatment for chronic posttraumatic headache. The impetus for this study comes from a large open-label case series in Iraq and Afghanistan Veterans with mTBI and posttraumatic headaches and data from a placebo-controlled trial evaluating use of prazosin for PTSD in Iraq and Afghanistan active-duty Service Members that found beneficial effect of prazosin for decreasing the frequency and severity of headaches, in addition to decreasing PTSD-related symptoms and improving the quality of sleep. The objectives of this study will be accomplished by conducting a randomized placebo-controlled double blind trial of prazosin vs placebo in 160 Iraq/Afghanistan active-duty Service Members and Veterans with persistent PTHAs.

15. SUBJECT TERMS

Headache, mTBI, prazosin, pain, clinical trial, placebo-controlled

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. **INTRODUCTION:**

   Headaches following combat-related mild traumatic brain injury (mTBI) are common, can be refractory to standard therapies, and may persist and worsen to become a debilitating chronic pain syndrome. The purpose of this study is to evaluate the centrally acting alpha-1 adrenoreceptor antagonist drug prazosin as a prophylactic treatment for chronic posttraumatic headache (PTHA). The impetus for this study comes from a large open-label case series in Iraq and Afghanistan Veterans with mTBI and PTHA and data from a placebo-controlled trial evaluating use of prazosin for PTSD in Iraq and Afghanistan active-duty Service Members that found beneficial effect of prazosin for decreasing the frequency and severity of headaches, in addition to decreasing PTSD-related symptoms and improving quality of sleep. The objectives of this study will be accomplished by conducting a randomized placebo-controlled double blind trial of prazosin vs placebo in 160 Iraq/Afghanistan active-duty Service Members and Veterans with persistent PTHAs.

2. **KEYWORDS:** headache, mTBI, prazosin, pain, clinical trial, placebo-controlled

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

  To evaluate the efficacy and safety of the alpha-1 AR antagonist drug prazosin as a prophylactic medical treatment for PTHAs, by conducting a randomized placebo-controlled double blind trial of prazosin vs placebo in Iraq/Afghanistan Service Members and Veterans with frequent persistent PTHAs.

  Specific Aim 1: To determine the effect of prazosin compared to placebo on HA frequency, HA severity and duration, use of abortive/analgesic medications, and HA-related disability.

  Specific Aim 2: To determine the effect of prazosin on sleep disturbance, PTSD symptoms, depressive symptoms, alcohol consumption, global cognitive function, health-related quality of life, and global clinical status.

- **What was accomplished under these goals?**

  Multiple site visits to Madigan Army Medical Center have been completed by Dr. Cynthia Mayer and the study team to discuss inclusion/exclusion criteria, protocol development, and study logistics. Study staff have been trained in study procedures.

  The subaward to Henry Jackson Foundation was executed 1/15/16.

  The VA Coordinating Center IRB application was approved in late April. VA R&D approval was obtained 5/5/16.

The study has had several setbacks regarding the Madigan regulatory process, including its multiple levels of review, but the application will finally be submitted in the next week. See below for additional details.

- **What opportunities for training and professional development has the project provided?**

  Our VA expert level MSW provided Skilled Clinical Interview for DSM 5 training to Madigan study staff.

- **How were the results disseminated to communities of interest?**

  Nothing to Report

- **What do you plan to do during the next reporting period to accomplish the goals?**

  Study staff continue to be trained in all study procedures. Case report forms will be reviewed and revised based on regulatory feedback. Study databases will be established. Recruitment strategies will be further refined. Recruitment materials will be developed, printed, and distributed.

4. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**

  Nothing to Report

- **What was the impact on other disciplines?**

  Nothing to Report

- **What was the impact on technology transfer?**

  Nothing to Report

- **What was the impact on society beyond science and technology?**

  Nothing to Report

5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

  Nothing to Report

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  The PTH study has had several setbacks with the Madigan regulatory process. The study team drafted the study documents in preparation for submission to the IRB. When the hard copy documents were nearly ready for submission, the IRB announced that the IRB was adopting a new mandated electronic management system. All documents were re-written in the new electronic format. When the documents were ready to be submitted, the Army suspended implementation of the

electronic management system. Hard copy documents then had to be completed on the newly drafted forms. The latest forms were only made available this past week. The application will finally be submitted as soon as all signatures are again obtained from the PI and study team members.

- **Changes that had a significant impact on expenditures**

  Nothing to Report
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  Nothing to Report
- **Significant changes in use or care of human subjects**

  Nothing to Report
- **Significant changes in use or care of vertebrate animals.**

  Nothing to Report
- **Significant changes in use of biohazards and/or select agents**

  Nothing to Report

6. **PRODUCTS:**

   Nothing to Report

- **Publications, conference papers, and presentations**

  Nothing to Report
- **Journal publications.** *List peer-r*

  Nothing to Report
- **Books or other non-periodical, one-time publications.**

  Nothing to Report
- **Other publications, conference papers, and presentations.**

  Nothing to Report
- **Website(s) or other Internet site(s)**

  Nothing to Report
- **Technologies or techniques**

  Nothing to Report
- **Inventions, patent applications, and/or licenses**

  Nothing to Report
- **Other Products**

  Nothing to Report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

Name	Role	PM	Contribution to project
Murray Raskind	PI	2.4 PM	PI
Elaine Peskind	Co-Investigator	1.2 PM	Scientific expertise
Beverly Scott	Madigan Site PI	1.2 PM	Scientific expertise
Cynthia Mayer	Co-Investigator	1.8 PM	Scientific expertise
Laura Crews	Research Coordinator	12.0 PM	Madigan site coordination
Jane Shofer	Biostatistician	8.4 PM	Study/database design
Wesley Chinn	Data Manager	3.1 PM	Data management
Dan Morelli	Research Coordinator	2.6 PM	VA site coordination
Rebecca Tzucker	Research Assistant	12.0 PM	IRB/study assistance

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  Elaine Peskind Other Support changes:

  No further support on:

  1. Pituitary dysfunction, behavioral symptoms, and quality of life after blast mTBI (I01 RX000509 Wilkinson), RR&D Merit Review Award , Department of Veterans Affairs, 4/1/12-3/31/16

  New Support on:

  1. Neurobehavior, Neuropathology, and Risk Factors in Alzheimer's Disease (T32 AG052354 Peskind, Kraemer), National Institutes of Health / NIA, 5/1/16-4/30/21, $320,000, 1.2 CM, Role: Director
  2. Chronic Traumatic Encephalopathy: Detection, Diagnosis, Course, and Risk Factors (U01 NS093334, Robert Stern), National Institutes of Health / NINDS, 12/15/15-11/30/22, $2,252,000, 0.6 CM. Role: Co-Investigator

- **What other organizations were involved as partners?**

  A subcontract to Henry Jackson Foundation provides support for personnel expenses for Laura Crews, our Research Coordinator at Madigan AMC.

8. **SPECIAL REPORTING REQUIREMENTS**

- **QUAD CHARTS:**

  please see attached

9. **APPENDICES:**

  none

Prazosin for Prophylaxis of Chronic Post-Traumatic Headaches in OEF/OIF/OND Service Members and Veterans with Mild TBI

W81XWH-15-2-0060

PI: Murray Raskind, MD **Org:** Seattle Institute for Biomedical & Clinical Research **Award Amount:** 3,967,000

Study Aims

- To determine the effect of prazosin compared to placebo on post-traumatic HA frequency, severity, duration, use of abortive/analgesic medications, and HA-related disability.
- To determine the effect of prazosin on comorbid sleep disturbance, PTSD symptoms, depressive symptoms, alcohol consumption, global cognitive function, health-related quality of life, and global clinical status (secondary outcome measures).

Approach

The proposed study is a prospective double-blind placebo-controlled RCT to evaluate the efficacy and safety of prazosin for prophylactic treatment of frequent persistent HAs following blast and/or impact mTBI in a convenience sample of SMs and Veterans who served in Iraq and/or Afghanistan. The total trial length is 22 weeks. Participants will be randomized 1:1 to prazosin or placebo. Recruitment and study procedures will be performed at Madigan/JBLM and VA Puget Sound.

R. L. Ruff and colleagues prescribed open label prazosin for nine weeks to 63 OEF/OIF Veterans who had experienced blast concussion mTBI(s) and had postconcussive headaches.[1]

	Baseline	Week 9
Headache Frequency (# / 4 weeks)	13.3 + 0.7	4.7 + 0.7 (p<0.001)
Headache Pain Intensity (0-10 scale)	7.4 + 0.2	4.0 + 0.2 (p<0.001)

The current study seeks to confirm this important observational study in a placebo controlled randomized trial of prazosin.

1. Ruff RL1, Riechers RG 2nd, Wang XF, Piero T, Ruff SS. For veterans with mild traumatic brain injury, improved posttraumatic stress disorder severity and sleep correlated with symptomatic improvement. J Rehabil Res Dev. 2012;49(9):1305-20.

Timeline and Cost

Activities	Year 1	Year 2	Year 3	Year 4	Year 5
Regulatory Approvals					
Preparatory Tasks					
Subject Recruitment					
Enter + Clean Study Data					
Data Analysis					
Write and submit results					
Estimated Budget ($K)	$779	$761	$782	$811	$833

Updated: 9/30/16

Goals/Milestones

☑ ☐ **Regulatory Approvals and Preparatory Tasks**
Completed / In progress

☑ ☐ **Recruitment and Retention Efforts** – Not yet initiated
- ☐ ☐ **Recruit and Randomize 30 Subjects**
- ☐ ☐ **Recruit and Randomize 100 Subjects**
- ☐ ☐ **Recruit and Randomize 175 Subjects**
- ☐ ☐ **Recruit and Randomize 200 Subjects**

☐ ☐ **Enter and clean study data** – Not yet initiated

☐ ☐ **Analyses and Evaluation** – Not yet initiated

☐ ☐ **Publish Results** – Not yet initiated

Comments/Challenges/Issues/Concerns – None at this time.

Budget Expenditure to date
Projected Expenditure:$779,000 Actual Expenditure:$375,000